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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,106	01/24/2005	Karl-Heinz Kogel	12810-00067-US	9243

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EXAMINER	
IBRAHIM, MEDINA AHMED	
ART UNIT	PAPER NUMBER
1638	
MAIL DATE	DELIVERY MODE
01/19/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,106	KOGEL ET AL.	
	Examiner	Art Unit	
	Medina A. Ibrahim	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/01/10 has been entered.

Claims 1-23 are pending and are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dsRNA comprising an isolated nucleic acid sequence encoding SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22 or the nucleic acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 3, 15, 17, 19, or 21; an expression cassette comprising said dsRNA sequence, and a method of generating or increasing at least one pathogen resistance in a plant/cell/part/or progeny thereof by transforming the plant/cells with a dsRNA nucleic acid sequence having one of said nucleic acid sequence, and transgenic plants comprising said nucleic acid sequences, does not reasonably provide enablement for a method that employs with a sense, antisense with

or without a ribozyme or a dsRNA with a nucleic acid sequence having less than 100% homology to any of the disclosed sequences or a nucleic acid encoding a polypeptide having less than 100% homology to any of the disclosed polypeptide sequences and having the same essential characteristics as the original sequence and capable of reducing activity or function of an endogenous NADPH oxidase in a transgenic plant, and a transgenic animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The claims are drawn to, *inter alia*, a method for generating or increasing a resistance to at least one plant pathogen which comprises reducing protein quantity, function or activity of a NADPH oxidase in a plant or tissue, organ, part or cell thereof, wherein the reduction is ensured by an NADPH oxidase sense or antisense nucleic acid sequence, wherein the NADPH oxidase comprises a polypeptide having at least 70% or 90% homology and having the same essential characteristics with the polypeptide sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22 or encoded by a nucleic acid sequence having at least 70% identity to 1, 3, 5, 7, 9, 11, 3, 15, 17, 19, or 21 , or encoded by a nucleic acid that hybridizes to any of the disclosed nucleic acid sequence or a part thereof under standard conditions. The claims are also drawn to said method wherein the reduction is ensured by introducing a NADPH oxidase antisense nucleic acid with or without ribozyme, a NADPH oxidase sense nucleic acid for co-suppression or a dsRNA NADPH oxidase into a plant cell, and regenerating a plant with increased pathogen resistance from the transformed plant cell. The claims are further drawn to

said method wherein the plant pathogen is from a specific fungal species, and said plant is from a specific monocot plant species or a dicot plant. The claims are also drawn to a recombinant dsRNA capable of reducing expression of a NADPH oxidase, said recombinant dsRNA comprising a sense strand comprising a sequence which is essentially identical to at least part of the sense transcript of a sequence encoding the NADPH oxidase and antisense strand which essentially complementary to the sense strand, or wherein the NADPH oxidase comprises a polypeptide or a nucleic acid as recited in the methods claims above; an expression cassette comprising at least part of a nucleic acid sequence encoding NADPH oxidase, operably linked to promoter in antisense and a vector comprising said expression cassette; and a transgenic organism including animals comprising said vector.

Applicant teaches the isolated nucleic acid sequences including SEQ ID NO: 1 identified as NADPH oxidase nucleic acids. Applicant also teaches SEQ ID NO: 1, from barley, has negative regulatory activity function upon attack by a powdery mildew of barley Blumeria graminis f.sp hordei (Bgh) and a method of reducing the NADPH oxidase expression in plant epidermal cells by using NADPH oxidase dsRNA comprising SEQ ID NO: 1 (Examples 1-4).

Applicant has not taught methods of reducing NADPH oxidase activity/amount/function in a plant other than the method of transforming the plant or the use of nucleic acids other than those encoding NADPH oxidase dsRNA having the ability to inhibit amount, function or activity of an endogenous NADPH oxidase. Applicant has not provided guidance for the obtention and use of the NADPH oxidase

sequences as broadly claimed or methods of their use in any organism including animals. Applicant has not taught other methods of reducing activity/function/amount of NADPH oxidase in a plant and that resulted in increased resistance to plant pathogens. Applicant teaches transient transformation of barley cells with dsRNA comprising the unmodified sequence of SEQ ID NO: 1 and the evaluation of the development of powdery mildew in said barley genotype.

Applicant has not provided guidance for any modifications to any of the disclosed sequences that resulted in DNA sequences encoding a polypeptide having at least 70% or 90% homology to any of the disclosed sequences and retaining the desired function. Applicant has not provided guidance for the use of the exemplified and non-exemplified NADPH oxidase sequences in organisms other than plants and microorganisms. Applicant has not provided guidance for a single variant of the disclosed sequences or a part thereof that is capable of reducing the amount, function or activity of an endogenous NADPH nucleic acid in a transgenic plant. The specification is completely silent with respect to how to use NADPH oxidase sequences in animals to induce disease resistance.

The state of the prior art is that the transformation of plants with inhibitory nucleic acids other than dsRNA is highly ineffective. For example, Chuang et al (PNAS (2000) 97(9): 4985-4990) teach that antisense, sense constructs and constructs with anti-sense and sense together, wherein sense or antisense constructs only had either no or weak genetic interference effects as compared to potent and specific genetic interference effects from dsRNA constructs (see Figure 1 and Table 1). Fire et al (US 6,

506, 559) teach the unpredictability and difficulties associated with the use of antisense technology for genetic inhibition such as delivery to the cell interior of specific single-stranded nucleic acid molecules at a concentration that is equal to or greater than the concentration of endogenous mRNA and the difficulty even with high doses of maintaining a sufficiently concentrated and uniform pool of interfering material in each cell. The cited reference states “(b)ecause antisense interference requires that the interfering material accumulate at a relatively high concentration (at or above the concentration of endogenous mRNA), the amount required to be delivered is a major constraint on efficacy." See also Wesley *et al.* Plant Journal (2001) 27(6), 581-590 who report the comparative efficiency of hairpin RNA, sense and anti-sense constructs at silencing a range of genes in a range of plant species with a clear indication that the efficiency for anti-sense constructs is typically about an order of magnitude lower than the efficiency for hairpin RNA (see for example, Table 1).

The state of the prior art teaches that reducing gene expression or transcript level does not necessarily result in reduction in gene product activity. Temple S.J. et al. (Down-regulation of specific members of the glutamine synthetase gene family in alfalfa by antisense RNA technology. Plant Mol Biol. 1998 Jun;37(3):535-47), teach that the ability of an antisense transcript to suppress gene expression and gene product activity depends on multiple variables which include but are not limited to gene copy number and the level at which gene expression is regulated. Tempe et al specifically teach introducing into alfalfa antisense gene constructs aimed specifically at two distinct classes of Glutamine synthetase 1 genes. While the gene constructs were effective in

lowering the corresponding transcript levels, transgenic alfalfa with up to 80% reduction in the transcript level corresponding to the two genes showed no reduction in Glutamine synthetase activity, or in Glutamine synthetase 1 polypeptide level (see at least abstract ; Figures 3, 5 and 6 ; page 541 column 2 and pages 543-545). In the instant case, the specification does not provide sufficient guidance with respect to how to express in a plant antisense transcripts such that NADPH oxidase activity, function or amount is inhibited, or how to express them such that disease resistance is increased as compared to a wild type plant. Absent such guidance one skilled in the art would have to test each of the myriad sequences encompassed by the claims for its effect on endogenous NADPH oxidase amount, function or activity in a transgenic plant.

The state of the prior art is that changing amino acids in a given protein can alter the original function. For example, Guo et al. (PNAS, 101 : 9205-9210, 2004, see page 9205, abstract; page 9206, table 1 ; page 9208, figure 1) teach that there is a probability factor of 34% that a random amino acid replacement in a given protein will lead to its functional inactivation. In the instant case, such a probability factor will be much higher as the claim encompasses changes of more than one amino acid in the protein encoded by SEQ ID NO: 1. Also see, Keskin et al. (Protein Science, 13:1043-1055, 2004, see page 1043, abstract) who teach that proteins with similar structure may have different functions.

Fourgoux-Nicol et al (1999, Plant Molecular Biology 40: 857-872) teach the identification of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and

0.1X SSC with 0.1% SDS at 65°C (page 859, left column, 2nd paragraph). Fourgoux-Nicol et al also teach that the probe and identified DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

The state of the art for isolating genes with specified function is highly unpredictable. Substantial guidance is required with respect to hybridization/wash conditions that would allow the specific isolation of the target genes. In the absence of such guidance, one skilled in the art has to proceed with trial and error experimentation to screen through the vast number of cDNA and genomic clones to identify those genes capable of reducing amount/activity/function of a NADPH oxidase in a plant cell, and to evaluate the ability of said genes to increase plant disease resistance against iron deficiency in any organism.

Furthermore, since the working examples disclosed in the specification are limited to the use of full-length dsRNA comprising antisense and sense sequences of SEQ ID NO: 1, the inhibitory ability of said dsRNA sequence cannot be extrapolated to antisense or sense sequences having 70% identity to a disclosed sequence or parts thereof, absent further guidance.

In *Genentech Inc* v. *Novo Nordisk A/S* (42 USPQ2d 1001 at p. 1005) the court stated "(p)atent protection is granted in return for an enabling disclosure of an invention,

not for vague intimidations of general ideas that may or may not workable…. . When there is no disclosure of. …or of any of the conditions under which a process can be carried out, undue experimentation is required….” See also *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd, 18 USPQ2d 1016 at page 1027*, where it is taught that the disclosure of a few gene sequences did not enable claims broadly drawn to any to any analog thereof.

Therefore, given the lack of guidance in the specification and in the prior art; the scope of the claims encompassing the use of NADPH sequences from any source to inhibit expression/level/amount of NADPH oxidase in any organism including animals; the unpredictability inherent in using antisense constructs to inhibit amount, activity or function of an endogenous target gene in a transgenic plant, and the nature of the invention, as discussed above, the claimed invention cannot be practiced throughout the broad scope , therefore, the invention is not enabled. See, In re Wands 858 F.2d 731, 8USPQ2nd 1400 (Fed. Cir.1988). See also, *In re Fischer, 166 USPQ 19 24 (CCPA 1970)* where the court determined that the scope of the claims must bear a reasonable correlation with the scope of the enablement.

Remarks

Claim are deemed free of the prior art of record.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Medina A. Ibrahim whose telephone number is (571)272-0797. The examiner can normally be reached on M-TH 8:00 am to 5:30 PM, and every other Friday from 8:00 AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MAI
1/14/2011

/Medina A Ibrahim/
Primary Examiner, Art Unit 1638